

## Decellularized liver matrix as a carrier for the transplantation of human fetal and primary hepatocytes in mice.

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### Public Summary:

Transplantation of primary hepatocytes has been shown to augment the function of damaged liver and to "bridge" patients to liver transplantation. However, primary hepatocytes often have low levels of engraftment and short survival after transplantation. To explore the potential benefits of using decellularized liver extracellular matrix (DLM) as a carrier for hepatocyte transplantation, DLM from the whole mouse liver was generated. Immortalized human fetal hepatocytes (FH-hTERT) or primary human hepatocytes were infused into DLM, which was then implanted into the omentum of immuno-deficient NOD/SCID/IL2r $\gamma$ <sup>-/-</sup> or NOD/SCID/MPS VII mice. The removal of endogenous cellular components and the preservation of the extracellular matrix proteins and vasculature were demonstrated in the resulting DLM. Bioluminescent imaging revealed that FH-hTERT transduced with a lentiviral vector expressing firefly luciferase survived in the DLM for 8 weeks after peritoneal implantation; whereas, the luciferase signal from FH-TERT rapidly declined in control mice 3–4 weeks after transplantation via splenic injection or with omental implantation after Matrigel encapsulation. Furthermore, primary human hepatocytes reconstituted in the DLM not only survived 6 weeks after transplantation, but also maintained their function, as demonstrated by mRNA levels of albumin and cytochrome P450 subtypes (CYP3A4, CYP2C9 and CYP1A1) similar to freshly isolated human primary hepatocytes. In contrast, when human primary hepatocytes were transplanted into mice via splenic injection, they failed to express CYP3A4, although they expressed albumin. In conclusion, decellularized liver extracellular matrix provides an excellent environment for long-term survival and maintenance of hepatocyte phenotype after transplantation.

### Scientific Abstract:

The transplantation of primary hepatocytes has been shown to augment the function of damaged livers and to bridge patients to liver transplantation. However, primary hepatocytes often have low levels of engraftment and survive for only a short time after transplantation. To explore the potential benefits of using decellularized liver matrix (DLM) as a carrier for hepatocyte transplantation, DLM from whole mouse livers was generated. Human fetal hepatocytes immortalized by telomerase reconstitution (FH-hTERTs) or primary human hepatocytes were infused into the DLM, which was then implanted into the omenta of immunodeficient nonobese diabetic/severe combined immunodeficient/interleukin-2 receptor gamma-deficient mice or nonobese diabetic/severe combined immunodeficient/mucopolysaccharidosis type VII mice. The removal of endogenous cellular components and the preservation of the extracellular matrix proteins and vasculature were demonstrated in the resulting DLM. Bioluminescent imaging revealed that FH-hTERTs transduced with a lentiviral vector expressing firefly luciferase survived in the DLM for 8 weeks after peritoneal implantation, whereas the luciferase signal from FH-hTERTs rapidly declined in control mice 3 to 4 weeks after transplantation via splenic injection or omental implantation after Matrigel encapsulation. Furthermore, primary human hepatocytes that were reconstituted in the DLM not only survived 6 weeks after transplantation but also maintained their function, as demonstrated by messenger RNA levels of albumin and cytochrome P450 (CYP) subtypes (CYP3A4, CYP2C9, and CYP1A1) similar to the levels in freshly isolated human primary hepatocytes (hPHs). In contrast, when hPHs were transplanted into mice via splenic injection, they failed to express CYP3A4, although they expressed albumin. In conclusion, DLM provides an excellent environment for long-term survival and maintenance of the hepatocyte phenotype after transplantation.